



A randomized double-blind trial of an interventional device treatment of functional mitral regurgitation in patients with symptomatic congestive heart failure—Trial design of the REDUCE FMR study

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Abstract The Carillon Mitral Contour System has been studied in 3 nonrandomized trials in patients with symptomatic congestive heart failure and functional mitral regurgitation. The REDUCE FMR study is a uniquely designed, double-blind trial evaluating the impact of the Carillon device on reducing regurgitant volume, as well as assessing the safety and clinical efficacy of this device. Carillon is a coronary sinus–based indirect annuloplasty device. Eligible patients undergo an invasive venogram to assess coronary sinus vein suitability for the Carillon device. If the venous dimensions are suitable, they are randomized on a 3:1 basis to receive a device or not. Patients and assessors are blinded to the treatment assignment. The primary end point is the difference in regurgitant volume at 1 year between the implanted and nonimplanted groups. Other comparisons include clinical parameters such as heart failure hospitalizations, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire (KCCQ), and other echocardiographic parameters. An exercise echo substudy will also be included. (Am Heart J 2017;188:167-74.)

Patients with functional, or secondary, mitral regurgitation (FMR) have worse hemodynamics, symptoms, and clinical outcomes compared with patients with cardiomyopathy without FMR.¹⁻¹¹ Although some have advocated for surgical treatment of secondary mitral regurgitation (MR), current data do not clearly demonstrate long-term benefits, and both European and US guidelines have given a 2b indication for the surgical treatment of secondary MR (who are not otherwise undergoing coronary artery revascularization).^{12,13} In current practice, this surgery is rarely performed unless

the patient is also undergoing coronary revascularization. Nevertheless, because reduction of FMR may ameliorate some of the associated negative consequences and/or symptoms, there remains interest in percutaneous means in treating this condition. There are currently 4 percutaneously placed devices approved for use outside the United States to treat MR, with MitraClip (Abbott, Santa Clara, CA) being the most commonly used device. Although MitraClip is used most commonly to treat FMR outside the United States, it is not approved for this indication in the United States.^{14,15} According to ClinicalTrials.gov, as of April 2015, 4 randomized trials of MitraClip to treat FMR have been launched—COAPT (ClinicalTrials.gov NCT01626079) in the United States, RESHAPE-HF (ClinicalTrials.gov NCT01772108) in Europe, Mitra-FR (ClinicalTrials.gov NCT01920698) in France, and MATTERHORN (ClinicalTrials.gov NCT02371512) in Germany.

The second most commonly implanted percutaneous MR device, the Carillon Mitral Contour System (Cardiac Dimensions Pty. Ltd. Sydney, Australia), has been studied specifically as a treatment of FMR and is currently being implanted commercially for this in several countries outside the United States. There have been 3 nonrandomized European safety and efficacy studies that suggested clinical and echocardiographic benefits with Carillon, with a favorable safety profile¹⁶⁻¹⁸ and favorable

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RCT No. NCT02325830

Submitted November 7, 2016; accepted February 25, 2017.

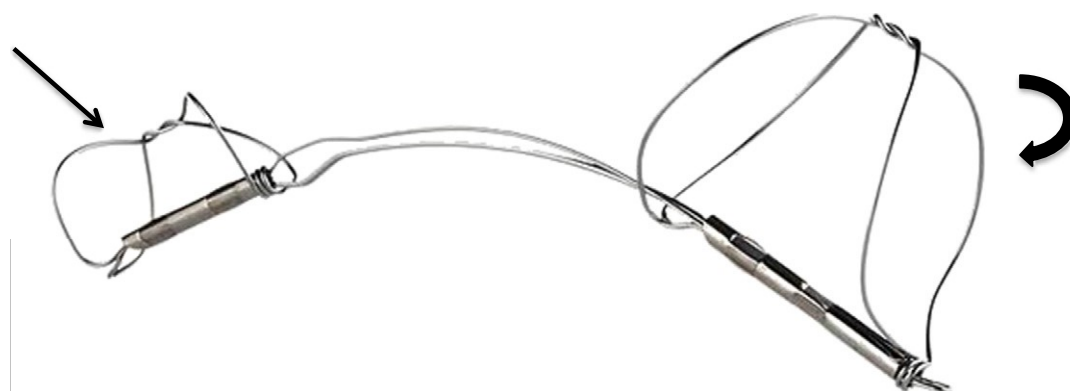
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0002-8703

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<http://dx.doi.org/10.1016/j.ahj.2017.02.032>

Figure 1

Carillon Mitral Contour System (mXE2) used in REDUCE FMR. Straight arrow points to the distal anchor. Curved arrow points to the proximal anchor.

economics.¹⁹ A uniquely designed, double-blind randomized trial to evaluate this device, the REDUCE FMR trial ([ClinicalTrials.gov](https://clinicaltrials.gov) NCT02325830), is currently underway in Europe, Australia, and New Zealand. This article describes the trial design and justification for the REDUCE FMR trial.

Methods

Device and procedure

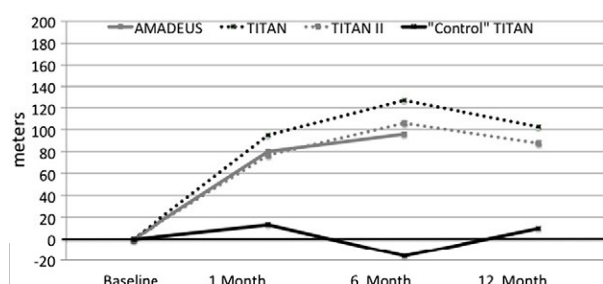
The mechanism and implementation of the Carillon Mitral Contour System have been described elsewhere.^{16,17} Briefly, this device takes advantage of the anatomic proximity between the coronary sinus/great cardiac vein and the posterior annulus of the mitral valve (albeit approximately 1 cm superiorly, on the left atrial side). The device is delivered through a proprietary curved 9F delivery catheter, via the right internal jugular vein. The device is composed of 2 self-expanding, nitinol anchors, connected by a nitinol curvilinear segment (Figure 1). There are a variety of anchor sizes (to accommodate different venous diameters) and overall device lengths of 60, 70, and 80 mm. After access is obtained in the great cardiac vein, the distal anchor is unsheathed and locked in a specific location, based on venous characteristics and coronary artery/venous relationships. The entire delivery system is then pulled back approximately 4 to 6 cm, providing a cinching force, and finally the proximal anchor unsheathed and locked. The amount of tension applied is dependent on the vein length, as well as other anatomic features, such as the relationship between the coronary vein and the circumflex coronary artery. The device may be recaptured periprocedurally if there is any compromise of a coronary artery, if there is insufficient reduction of MR, or if the

device is not optimally placed. If, however, everything is satisfactory, the device is detached from the delivery system and the procedure completed. The procedure may be done with transesophageal or transthoracic echocardiography to evaluate periprocedural changes in MR and mitral annular dimensions, using either general anesthesia or conscious sedation.

Prior clinical experience

Three European safety and efficacy studies have been completed, using different iterations of the device.¹⁶⁻¹⁸ In the TITAN study,¹⁷ patients who had a device placed and then removed had identical follow-up to patients receiving devices—for 1 year with clinical and echocardiographic assessments. Thus, this group provided a nonrandomized, pseudo-control group. As expected, this pseudo-control group did not show any clinical or echocardiographic benefits, in contrast to the group who received a Carillon implant (Figures 2 and 3). These benefits included a significant reduction in MR and left ventricular (LV) dimensions, as well as improvements in New York Heart Association (NYHA) status, 6-minute walk test (6MWT) duration, and KCCQ evaluations. However, asymptomatic wireform fractures were seen, predominately in a specific location in the proximal anchor, near the locking mechanism. The TITAN II trial was undertaken to evaluate a newer iteration of device with design changes to specifically reduce this risk of wireform fracture.¹⁸ Similar clinical and echocardiographic findings were seen in TITAN II to those in TITAN, without the incidence of wireform fractures of the strain relief portion of the proximal anchor. Therefore, it was decided to move forward with a pilot randomized trial using the version of the device used in TITAN II.

Figure 2



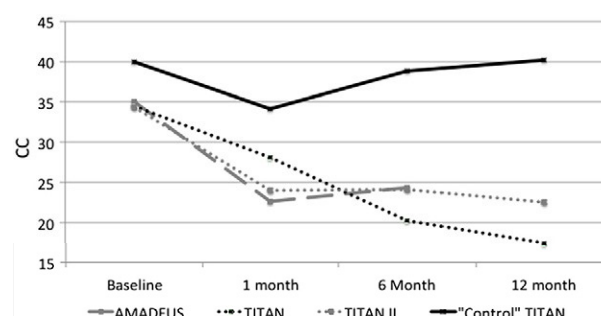
Change in 6MWT from baseline to 1, 6, and 12 months in AMADEUS, TITAN (implanted patients), and TITAN II,¹⁶⁻¹⁸ as well as the nonimplanted "control" patients from TITAN. AMADEUS only had 6-month follow-up. All 3 studies showed similar improvements in patients implanted with Carillon devices, with no improvement seen in the nonimplanted cohort of TITAN.

The 3 trials enrolled 36 to 53 patients each, with successful implants in 30 to 36 patients (implant rate of 63% in AMADEUS, 68% in TITAN, and 83% in TITAN II). Each study showed an excellent safety profile, given the high risk of patients being treated, with a single death in each of the latter 2 trials being the only major adverse event in each study. None of the deaths in any of the trials were device related, but occurred weeks after the procedures. It may be noted that the 1-year mortality rate for patients with congestive heart failure is ~23%,²⁰ which translates to a 1.9% monthly mortality—identical to the 30-day mortality in the 3 Carillon trials.

As mentioned above, each trial showed clinical benefits in patients treated with the Carillon device, which were not seen in the pseudo-control population of TITAN. These include a reduction in NYHA class and improvements in 6MWT (Figure 2). In AMADEUS and TITAN, patients were also evaluated with the KCCQ and significant improvements were observed, again not seen with the pseudo-control group in TITAN.

Of course, the possibility of a placebo effect in the group receiving a device, or a nocebo effect in the TITAN population not receiving a device, could have had an impact on these measurements. However, objective measurements of improvement were also seen in patients receiving the Carillon device, with a decrease in mitral annular dimensions, reductions in quantitative assessments of MR, and favorable LV remodeling (Figure 3). These improvements were not seen in the pseudo-control TITAN population; indeed, those patients showed continuing deterioration in ventricular geometry. Nevertheless, to minimize the impact of a placebo/nocebo effect, it would be useful to evaluate the Carillon therapy

Figure 3



Regurgitant volume at baseline and 1, 6, and 12 months in AMADEUS, TITAN, and TITAN II (AMADEUS was limited to 6-month follow-up).¹⁶⁻¹⁸ Similar reductions in MR were seen in implanted patients in each of the 3 studies, with no reduction seen in the nonimplanted "pseudo-control" group in TITAN.

in a blinded randomized trial. Although there are ethical considerations to subjecting patients to a procedure in which nothing specifically therapeutic is provided, recent studies have emphasized the potential value of blinding in clinical device trials, when feasible.²¹ Notably, in a recent blinded randomized trial of renal denervation in patients with refractory hypertension, no increase in benefit was seen in patients who received active therapy, in comparison with the group who received no denervation.²² This was in marked contrast to prior registry and nonblinded studies, in which more impressive reductions in blood pressure were seen with denervation.^{23,24} This highlights the value of a blinded randomized trial; however, such a trial has never been performed in patients undergoing treatment of MR and is not a component of other current randomized trials of therapy for MR (COAPT [ClinicalTrials.gov NCT01626079], Mitra-FR [ClinicalTrials.gov NCT01920698], and MATTERHORN [ClinicalTrials.gov NCT02371512]). Funding for this study was provided for by Cardiac Dimensions, the manufacturer of the Carillon Mitral Contour System.

REDUCE FMR trial design and objectives

The REDUCE FMR trial is being conducted in accordance with the International Standard ISO 14155:2011; recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions; Good Clinical Practice: Consolidated Guidance (ICH E-6); and any regional or national regulations, as appropriate.

The objective of this prospective, multicenter, randomized, double-blind trial is to assess the safety and efficacy of the Carillon Mitral Contour System in FMR associated with heart failure, compared with a control arm treated with standard medical treatment according to heart failure guidelines. The study is being performed in approximately 20 centers in Europe, New Zealand, and Australia. European countries include Great Britain, the Netherlands, Germany, France, Poland, and Czech Republic. Currently, there are no guideline-recommended interventional therapies beyond medical therapy for patients with secondary MR, other than coronary artery revascularization when indicated, although some patients will be eligible for cardiac resynchronization therapy (CRT). Patients requiring, or undergoing recent, coronary artery revascularization are not enrolled in REDUCE FMR.

Subject screening and enrollment

Patients to be evaluated are those with functional MR (grades 2+ to 4+), dilated ischemic or nonischemic cardiomyopathy, symptomatic congestive heart failure (NYHA classes II-IV) with an impaired 6MWT of 150 to 450 m, which were criteria for the prior studies. In addition, as in the prior studies, patients are required to have objective evidence for systolic dysfunction with a LV ejection fraction ≤ 40 , as well as an enlarged, with a LV end-diastolic diameter > 55 mm. However, based partly on the Mitral Valve Academic Research Consortium recommendations,^{25,26} the ejection fraction cutoff has been revised to up to 50% in a modification of the study protocol (which is also being used in the COAPT study).

Patients are to be on a stable medical regimen for a minimum of 3 months. This regimen is to include a β -blocker, either an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker (or documented intolerance to these respective medications), as well as a diuretic. Although adjustments of the diuretic may occur over the preceding 3 months, the patient should be on an optimal and stable dose of the other medications for at least 2 months.

Exclusion criteria include hospitalization within the prior 3 months for a myocardial infarction, coronary artery bypass graft surgery, or unstable angina. Additional exclusions include percutaneous coronary intervention within the prior 30 days, or anticipated cardiac surgery or percutaneous coronary intervention within the upcoming 30 days. Patients are not to be enrolled if there is a need for cardiac hemodynamic support, either medically or mechanically, within the past 30 days. Patients are not to have a coronary stent at a site that might be crossed by the coronary sinus/great cardiac vein, most notably in the circumflex coronary artery, nor are they to have an indwelling pacemaker lead in the coronary sinus. Patients are excluded if they have had prior mitral valve surgery, significant organic mitral valve pathology, or severe

mitral annular calcification. Left atrial thrombus is an exclusion, as is renal insufficiency with a creatinine > 2.2 mg/dL (> 194.5 μ mol/L).

It is recognized that only a minority of patients eligible for CRT devices actually receive one,²⁷ despite the data and recommendations supporting its use, so placement of a CRT device cannot yet be considered standard of care. It is further recognized that there is a wide disparity in the adoption of CRT therapy, so each site determines whether CRT therapy should be used instead of including a patient in REDUCE FMR, in particular in patients who do not have a guideline-directed class I indication for a CRT device.

Echocardiography

The echocardiographic techniques are guided by an echo core laboratory, who make blinded preprocedure and postprocedure quantitative assessments. Two-dimensional echocardiography is undertaken at baseline and follow-up. After the selection echocardiogram, subsequent studies are undertaken at device implantation to facilitate device placement and assess changes in MR severity, discharge, and months 1, 6, and 12. The procedural echo may be TEE or TTE, depending on the site preference. A transesophageal echocardiogram is done just before or as part of the procedure, if the patient has atrial fibrillation with attendant risk of an atrial appendage thrombus.

Because echocardiographic interpretation at the FMR sites has important implications on recruitment, site sonographers have undergone training to ensure familiarity to imaging protocols detailed in the instruction manual, as well as attending a personalized Web-based training, and submission of a training study echo with all required views. Only after attainment of the required standard are sonographers deemed qualified to acquire study echocardiograms.

Standard echocardiographic equipment is used, including harmonic imaging with a 3.5-MHz broadband transducer, with capture of at least 3 beats per view (10 beats/view in atrial fibrillation). Blood pressure is gathered before the test in both arms, after the subject has been resting for 5 minutes at baseline. Echocardiograms are acquired in the left lateral decubitus position, with the degree of lateral rotation dependent on image and window. A standard echocardiographic study is performed (Appendix A), with particular focus on the quantitation of MR and optimizing endocardial border definition of left-sided chambers. An exercise echocardiographic substudy is also being done, to assess LV volumes and MR responses to exercise.

To facilitate LV quantitation, care will be paid to the display and measurement of the maximum cavity length in apical imaging planes, to maintain the same length in all apical images to avoid fore-shortening (especially

A2C). As speckle strain performs optimally at moderate frame rate (50-70 fps), care is taken to avoid excessive narrowing of the sector angle. Because the greatest limitation of sequential 2D echo is the use of a different imaging window/angle from the baseline study, sonographers performing review studies will review the baseline study on a workstation, if possible to have this image close to the monitor to optimize the acquisition. Comments about the image settings and window will be saved on the worksheet.

Mitral regurgitation quantitation is performed using color Doppler. Images are optimized for color gain and color scale (to ensure 3 portions—PISA (Proximal Isovelocity Surface Area), vena contracta, and body of MR jet are clear).

An independent core echocardiogram laboratory is being used for blinded interpretation of the studies. Although an imaging artifact may occasionally be noted above the mitral annulus as a result of the coronary sinus-based device, calcifications can occasionally provide similar artifacts, which facilitates blinding. In addition, the measurements will be interpreted by the core laboratory without awareness of which study is being evaluated.

Primary and secondary end points

The primary efficacy end point is to demonstrate a statistically significant improvement in regurgitant volume associated with the Carillon device at 12 months, relative to the control population.

Secondary end points regarding safety and efficacy are also being evaluated, including mortality and hospitalizations for congestive heart failure. Six-minute walk test and LV anatomic dimensions are being evaluated at 1, 6, and 12 months. Patients with an ejection fraction >40% will be evaluated separately, as they are less likely to show a remodeling benefit. This study is double blind, with the patients and the assessors of these end points to be blinded as to the randomization category of the patient.

In addition, this study allows for the evaluation and suitability of the blinding procedure before embarking on a pivotal study.

Blinding and randomization

Part of the evaluation for the suitability of receiving a Carillon device includes invasive measurements of the coronary sinus/great cardiac vein. The vein must be long enough to place a 6-cm-long device, and pull a minimum of 3, and preferably 4 to 6 cm of cinching. Hence, the minimum length of usable vein is 9 and preferably 10 cm. In addition, adequate venous diameter dimensions for the anchors must be present. A small subset of patients, 2 in AMADEUS (4.2%), 4 (6.2%) in TITAN, and 2 (2.9%) in TITAN II, were found to have venous anatomy unsuitable for the Carillon Mitral Contour System, after venography was performed. Although computed tomo-

graphic (CT) imaging was done in AMADEUS, in part, to assess the vein suitability for the procedure, such imaging was not found to be suitable to replace invasive venography.

Because venous angiography needs to be done to assess if the dimensions are suitable for the Carillon device, this provides an opportunity for blinding as a key component of the REDUCE FMR trial. After patients have met key inclusion criteria and signed an informed consent form, they are brought to the cardiac catheterization laboratory. Patients are either under general anesthesia or wearing headphones and eyeshades to mask the procedure being performed. Vascular access is obtained in the right internal jugular vein for venography and arterial access for coronary angiography. The coronary sinus is engaged with a purposed designed 9F delivery catheter. Quantitative venography and coronary arteriography are performed. If the patient has suitable venous dimensions for a Carillon device and no coronary artery disease requiring revascularization, randomization is undertaken at that time.

Blinding is facilitated by the rapid delivery and deployment of the device (approximately 10 minutes) after venography has been performed. The bulk of the time doing the procedure is in preparation and accessing of the coronary venous system. Therefore, even the patient undergoing the procedure under conscious sedation should not be able to detect whether additional time was used to deploy a device.

In the AMADEUS study, CT angiography was performed before the Carillon procedure for several possible benefits. First was to establish venous-arterial relationships, to assess whether it was possible to predict which patients would be at risk for coronary artery compromise with the Carillon device. However, because of the complexity of arterial-venous relationships and because of differences in compliances of the nonvascular tissues in the vicinity, the CT images were not able to predict which patients would have coronary compromise with tensioning of the Carillon device. The second potential value of CT imaging was to assess venous dimensions to help with selecting appropriate-sized devices and identify which patients had suitable venous dimensions for the Carillon procedure. However, the dimensions seen with CT imaging in that study did not correlate well with quantitative measurements with invasive venography. Third, it was thought that perhaps measurements on CT imaging of the distance of the coronary sinus to the mitral annulus might be an important predictor of efficacy of the coronary sinus-based device. However, an unpublished analysis of data from AMADEUS failed to show any relationship between distance of the coronary sinus to the annulus and efficacy, in any plane or at any level. Therefore, CT imaging was not included in this study.

Randomization is done via computerized Web portal and is stratified by site in a randomized permuted blocks

design. Randomization is done in a 3:1 allocation, with 3 of 4 patients allocated to the Carillon device treatment arm. Patients randomized to no device undergo similar procedural assessments (including periprocedural echo assessments) to ensure that patients under conscious sedation are kept blinded to group assignment. Patients randomized to the treatment arm undergo the Carillon procedure as described above.

An additional unique feature of this study design is the 3:1 randomization scheme. This was done to encourage patients to agree to participate in the study, because there is a greater chance of getting active treatment. Because the patient is blinded, this should not have any impact on a placebo/nocebo effect. An additional advantage of the 3:1 randomization is the increased data to be gathered on implanted patients, which may have mechanistic value (such as impact of device length, location, amount of tension, etc). The 3:1 randomization does increase the overall sample size assumptions by approximately 30%, however, to allow for similar statistical power compared with a 1:1 randomization.

Assessors blinded to the patient's group allocation do clinical assessments for NYHA, 6MWT, and KCCQ. In addition, backup blinded personnel are trained and available in case the primary assessor becomes unblinded. An independent core echocardiography laboratory does echocardiography assessments, as described above.

Because subjects may visit non-study-related physicians during their participation in this study, for example, for emergency or standard care, each subject is given a study participant card with instructions to present the card to health care providers at any non-study-related visit. The subject participant card is to alert non-study medical personnel that the subject is in a blinded clinical study and request that they maintain the study blind whenever possible. Furthermore, the study subjects are questioned at every follow-up to ask if they have become unblinded and, if so, the reason associated with becoming unblinded.

The study is being monitored by a Data and Safety Monitoring Board and events are being evaluated by a Clinical Events Committee.

Statistical considerations

Reduction in regurgitant volume was selected as a primary end point, as it is a quantitative measurement of the mechanistic impact of the Carillon device—reducing MR. Although prior studies (such as EVEREST II²⁸) used MR grade as the primary means to assess MR, the recommendations of echocardiography experts are to use quantitative parameters rather than MR grade.^{4,12,29,30} In addition, because regurgitant volume is a continuous variable, this allows for more robust means of statistical analyses.

The power of the study was based on an 80% chance of identifying a reduction in regurgitant volume in the

treatment group compared with control group at 1 year. In the TITAN and TITAN II studies, the mean reduction in mitral regurgitant volume at 12 months was 14.1 mL (vs 2.4 mL in the non-device arm of TITAN). Because it is anticipated that approximately 15% of patients assigned to device will not receive one due to coronary artery compression (based on the experience in the above-mentioned trials, although commercial experience has had a greater implant rate³¹), the hypothesized mean reduction in regurgitant volume from baseline to 1 year will be 12.4 mL.

Several assumptions regarding compliance have been factored in. It is assumed that there will be ~25% loss to follow-up, in part due to mortality. The primary analysis will be done using Student *t* test comparison of means, using a 2-sided level of significance of .05. It is estimated that 76 evaluable patients will need to be randomized. To factor in patient dropout and noncompliance, 120 patients will be randomized.

In patients who do not have the final 12-month echo, the regurgitant volume from their last follow-up echo (at 1 or 6-month follow-up) may be used instead, to minimize impact of patient dropout or noncompliance, and will be provided as supportive sensitivity analysis. Because patients receiving devices in the prior studies showed greater improvement in MR over time, this imputation of data should bias away from a beneficial effect of a device. Patients who die before their first 1-month follow-up will be considered to have no improvement in their regurgitant volume compared with baseline.

Crossover registry and exercise echocardiography substudy

Patients who do not receive a device may be offered one at the end of the 1-year follow-up (crossover registry). This is also a way to incentivize patients to agree to participate in the study. Patients who still meet the criteria for implantation of the Carillon device and are adjudged suitable by the site principal investigator are offered the chance to participate in this registry and will be followed up for 1 month after the procedure to evaluate for safety events.

An exercise echo substudy is being done in a limited number of selected centers. Patients who provide additional consent for this substudy undergo a symptom-limited graded exercise using a supine bicycle, increasing the workload by 25 W every 3 minutes. Measurements done at each study include effective regurgitant orifice area, mitral annular dimensions (diameter and area), and pulmonary artery pressure from the tricuspid regurgitant jet. These studies will be done at baseline, and at 1-, 6-, and 12-month follow-up visits.

The authors are solely responsible for the design and conduct of this study, all study analyses, and the

drafting and editing of the manuscript and its final contents.

Considerations

Several choices were made regarding patient selection and eligibility that may have an impact on the study findings. First, it was decided to include patients with lesser degrees of MR (2+ MR grade). This has the potential to dilute the results of the primary end point, as patients with lesser degrees of MR may be expected to have a smaller absolute benefit. However, all patients included in this study were symptomatic, and therefore, it was clinically justifiable to treat these patients to ameliorate their symptoms. Patients with 2+ MR were included in prior studies of Carillon, and analyses of these patients suggested that there were similar relative improvements in MR and symptoms in patients with 2+ MR compared with patients with 3-4+ MR at baseline, although the absolute numbers were lower (due to less regurgitant volume at baseline). Second, it was decided to add patients who had more normal baseline ejection fractions, up to 50%, from the 40% originally as the upper boundary, and the level chosen in the prior Carillon studies. Because patients with higher ejection fractions have more normal LV volumes, the inclusion of such patients has the potential to reduce the ability to detect favorable ventricular remodeling, an important finding in earlier trials of Carillon. However, it was noted that a significant proportion of patients being treated commercially with Carillon had normal or near-normal ejection fractions, so this population of patients is important to study. In addition, the COAPT trial of MitraClip for functional MR includes patients with an ejection fraction up to 50%, establishing a precedent.

Summary

The REDUCE FMR study is a double-blind randomized trial of patients with secondary MR. A key characteristic of this unique trial is the double-blind, placebo-controlled design of the study, which should allow for greater confidence in detecting any differences in subjective secondary end points. The primary end point is the objective impact of MR reduction when the Carillon Mitral Contour System is used to treat symptomatic patients with MR secondary to an underlying cardiomyopathy. Thus, the REDUCE FMR is a mechanistic study, evaluating the impact of the Carillon device in improving MR, rather than a clinically powered end point. Information from this study will inform the design and power of a clinically relevant pivotal trial. This is in keeping with the spirit of the Mitral Valve Academic Research Consortium principles.²⁶

Appendix A

Appendix Table 1. Measurements/calculations

M-mode	Aortic root and left atrial AP diameter (Ao/LA) Left ventricular end-diastolic diameter (LVEDD) Left ventricular end-systolic diameter (LVESD) Septal wall thickness (diastole) (IVS) Posterior wall thickness (diastole) (PW)
2D	LVOT diameter Left ventricular end diastolic volume (LVEDV and length); 4- and 2-chamber Left ventricular end systolic volume (LVESV and length); 4- and 2-chamber Left ventricular ejection fraction (EF) and stroke volume (SV) Left atrial biplane volume (4- chamber and 2-chamber) (LAV) Mitral annulus diameter (4-chamber) and area Global longitudinal strain and strain rate (GLS) IVC dimension (and with sniff)
Color	Effective regurgitant orifice area (EROA), regurgitant volume Vena contracta/PISA MR jet area/left atrial area (4-chamber and 2-chamber) MR grade
Doppler	Mitral E, A velocities, E/A ratio, deceleration time Isovolumic relaxation and contraction times (IVRT and IVC) Aortic and mitral valve opening and closing Aortic valve velocity and velocity time integral (CW) (VTI) LVOT velocity and velocity time integral (PW) (VTI) RVOT velocity and velocity time integral (PW) (VTI) Tricuspid valve regurgitant velocity (CW) (TR) Cardiac output
Tissue Doppler	Mitral CW Doppler (4-chamber) Left ventricular S', E', and A' velocities Right ventricular S' velocity Left ventricular filling pressure (E/E')
<i>Exercise echocardiography (substudy at some centers)</i>	
Rest/stress 2D	Left ventricular end diastolic volume (4-chamber and 2-chamber) (LVEDV) Left ventricular end systolic volume (4-chamber and 2-chamber) (LVESV) Left ventricular EF and stroke volume (SV) Left atrial biplane volume (4-chamber and 2-chamber) (LAV) Mitral annulus diameter (4-chamber) and area
Rest/stress color	Effective regurgitant orifice area (EROA) Vena contracta/PISA MR jet area/Left atrial area (4-chamber and 2-chamber) MR grade
Rest/stress Doppler	Tricuspid valve regurgitant velocity (CW) (TR)

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